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Alagille Syndrome With Interstitial 20p Deletion Derived From Maternal ins(7;20)

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We present a 6-year-old Chinese boy with Alagille syndrome and an interstitial 20p deletion, with a karyotype of 46,XY,der(20)dir ins(7;20)(q11.23;p11.23p12.2 or p12.2p13)mat. He had a peculiar face and suffered from congenital heart disease, growth retardation, severe cholestasis, hepatosplenomegaly, and impaired renal function. The karyotype of his mother showed a balanced translocation, 46,XX,dir ins(7;20)(q11.23; p11.23p12.2 or p12.2p13), and her phenotype was normal. His dead elder brother was highly suspected as another victim of Alagille syndrome. The findings in the present family suggested that if Alagille syndrome is a single gene defect, the putative gene responsible for the syndrome would not be located at the insertion breakpoints but located within the deletion extent.

KEY WORDS: Alagille syndrome, arteriohepatic dysplasia, chromosome 20, chromosome deletion, chromosome insertion

INTRODUCTION

Alagille syndrome, or arteriohepatic dysplasia, is a multiple malformation syndrome characterized by intrahepatic biliary duct hypoplasia, peculiar face, peripheral pulmonary artery hypoplasia or stenosis, butterfly-like vertebral defects, and posterior embryotoxon [Watson et al., 1973; Alagille et al., 1975, 1987]. Since Byrne et al. [1986] reported a 20p deletion in an infant with Alagille syndrome, the knowledge about the association of Alagille syndrome with 20p deletion has been increasing. Here we present a 6-year-old Chinese boy with Alagille syndrome and an interstitial 20p deletion which was derived from a maternal chromosome insertion.

CLINICAL REPORT

The propositus was the second offspring of nonconsanguineous Chinese parents. Their first son had frontal bossing, hypertelorism, and apparently low-set ears, tetralogy of Fallot, and hypoplasia of intrahepatic bile ducts, and died at age 3 years of liver failure. There was no history of significant medical problems in the parents. Their facial appearances were normal. The liver function tests, renal function tests, and sonograms of the heart, liver, and kidneys of the patient's mother all yielded normal results.

He was born at 38 weeks of gestation after an uneventful pregnancy. His birthweight was 2,850 g. Severe abdominal distention was found at birth. Meconium peritonitis was diagnosed at surgery on the second day of life. Subsequently, he had suffered from persistent jaundice, and xanthomatosis developed at age 2 years. The wedge biopsy of the liver performed at the previous medical center at age 4 years showed paucity of interlobular bile ducts, and then Alagille syndrome was diagnosed.

He was first admitted to our hospital at age 6 years for pre-transplant evaluation. Physical examination showed a markedly short and thin child, height of 90 cm (−4.8 SD), weight of 12 kg (−2.4 SD), and head circumference of 47 cm (−3.1 SD). The conjunctivae were anemic and the scleral icterus was evident. He had frontal bossing (Fig. 1), mild hypertelorism, anti-mongoloid slant of palpebral fissures, depressed nasal bridge, and prominent nasal root. A grade II/VI systolic ejection murmur was heard over the aortic and the pulmonary areas. The abdomen was distended with engorged superficial veins. The liver was firm and enlarged, and its edge was 4 cm below the right costal margin. An edge of the spleen was 10 cm below the left costal margin. He had bilateral genu valgus, clubbing of fingers and toes, and symmetric swelling with local heat of both knees and ankles. There were many xanthomas over the extensor areas of limbs. His development of motor and language was delayed. His IQ score on Stanford-Binet Intelligence Scale was 88.

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Fig. 1. Facial appearance at age 6 years.

Fig. 2. Roentgenogram of both knees showing severe osteopenia, soft tissue swelling with widened joint space, and metaphyseal widening and fraying.

His hemoglobin level was 9.6 g/dl, albumin was 2.8 g/dl, total bilirubin was 11.8 mg/dl, direct bilirubin was 7.0 mg/dl (the total bilirubin 28.9 mg/dl, and the direct bilirubin 21.2 mg/dl 7 months later), SGOT was 152 IU/l, SGPT was 166 IU/L, alkaline phosphatase was 1,403 IU/l, gamma-glutamyl-transpeptidase was 465 IU/l, cholesterol was 476 mg/dl, and triglyceride was 256 mg/dl. Antibodies for hepatitis A virus, hepatitis D virus, and HIV-1 were absent. However, antibody for hepatitis B surface antigen was present. Significant proteinuria (>3 g/24 hr) and impaired creatinine clearance were found thereafter.

Results of thyroid function tests were normal. The insulin tolerance test showed a peak growth hormone of 28.91 ng/ml. His serum level of 25-hydroxy vitamin D was 5.0 ng/ml, c-PTH was 0.33 ng/ml, calcium was 10.6 mg/dl, and phosphorus was 2.7 mg/dl. Roentgenography of the skeleton demonstrated severe osteopenia, metaphyseal widening with fraying, delayed bone age (only at 3 years of age), and soft tissue swelling with widened joint space of both knees (Fig. 2). Synovial fluid of the right knee was orange, sticky, and transparent. It showed negative crystal stain, WBC of 603/mm^3, neutrophil of 70%, and negative culture. No butterfly-like vertebral defects was noted. MRI of the brain showed hypoplasia of the corpus callosum. Echocardiogram disclosed a mild valvular aortic stenosis and pulmonary artery stenosis. Sonogram of the abdomen disclosed increased echogenicity of the liver and both kidneys, and a remarkable dilatation of the portal and splenic veins. Ophthalmologic assessment confirmed the presence of bilateral posterior embryotoxon. The second liver biopsy documented intracellular and intracanalicular cholestasis, ballooning degeneration of the hepatocytes, mild mononuclear cell infiltration, and fibrosis in the portal areas with reduced number of bile ducts, but no evidence of cirrhosis. Renal biopsy showed marked mesangial cell proliferation with lobular accentuation, glomerulosclerosis (glomeruli: 3/14), occasional foamy cell in mesangium, and vacuolation of visceral epithelial cells.

CYTOGENETIC FINDINGS

Cytogenetic analysis using GTG banding, at an approximately 700- to 800-band level, of peripheral blood lymphocytes demonstrated a karyotype of 46,XY, der(20)dir ins(7;20)(q11.23;p11.23p12.2 or p12.2p13) mat in the patient (Fig. 3) and 46,XX,dir ins(7;20)(q11.23;p11.23p12.2 or p12.2p13) in his mother (Fig. 4). Chromosomes of his grandfathers (I-1 and I-3), maternal grandmother (I-4), father, and aunt (II-2) were all normal (Fig. 5). His dead elder brother (III-1) was not available for testing.

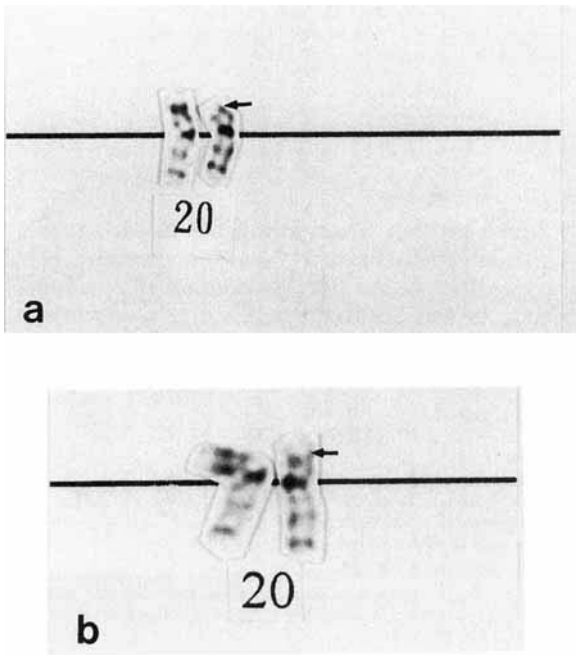
DISCUSSION

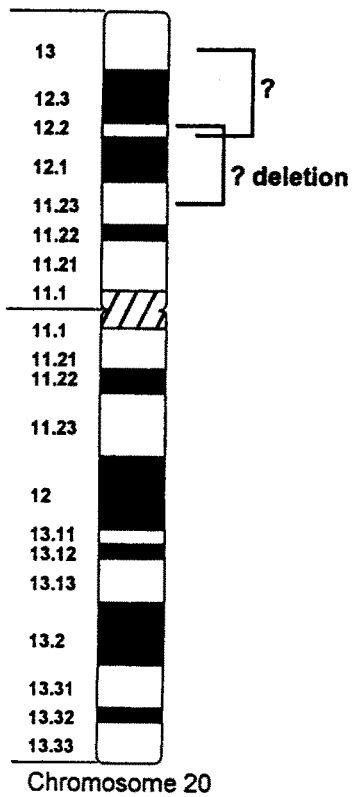
Alagille et al. [1987] described severe and mild forms of Alagille syndrome based on five major manifestations and less frequently associated abnormalities among 80 cases. Our patient had four of the five major manifestations of this syndrome, i.e., chronic cholestasis with hypoplastic interlobular bile ducts, valvular aortic stenosis and pulmonary artery stenosis, posterior embryotoxon, and a peculiar face. Two other anomalies were present, i.e., growth hepatosplenomegaly and signs of portal hypertension. Synovial fluid study of the right knee showed a mildly aseptic inflammation. X-ray examination and laboratory tests showed the presence of rickets which may occur in patients with hepatic disease. It has been reported that growth-retarded children with Alagille syndrome were insensitive to growth hormone with low insulin-like growth factor-I (IGF-I) [Bucuvalas et al., 1993]. Unfortunately, IGF-I test was not available at our laboratory. The patient also had documented hypoplasia of the corpus callosum by brain MRI, which had never been mentioned in Alagille syndrome patients. This may play a role in the mental retardation of this patient.

It has been stated that Alagille syndrome is a form of biliary paucity with a good prognosis. In our patient, the morbidity due to this syndrome is serious. He suffered from cholestasis, nephrotic syndrome with renal function impairment, and severe growth retardation. His condition has compromised his life enough to prompt a liver transplantation and possibly a concurrent kidney transplantation. Liver transplantation can be efficacious against an end-stage liver disease in patients with Alagille syndrome. Two to nine years after surgery, Tzakis et al. [1993] reported a 57% survival rate in 23 children. Our patient is awaiting a suitable donor.

An autosomal dominant transmission of Alagille syndrome with reduced penetrance and variable expressivity was suggested from many pedigrees [Watson et al., 1973; LaBrecque et al., 1982; Shulman et al., 1984], although the nature of the genetic defect has not clearly been established. Since Byrne et al. [1986] presented a 20 bp deletion in an infant with Alagille syndrome, an increasing number of cases has been reported. It was proposed that Alagille syndrome was a contiguous gene syndrome and was assigned to 20p11.23-p12.2 [Schnittger et al., 1989; Legius et al., 1990; Anad et al., 1990]. We find that 17 cases of the 20 bp deletion have been reported to date. Most of them had a de novo deletion. The first report by Loiodice et al. [1970] lacked detailed cytogenetic and clinical descriptions. Another 16 cases were reviewed by Anad et al. [1990] and Teebi et al. [1992]. Spinner et al. [1994] described another interesting three cases of Alagille syndrome in a two-generation family with a cytogenetically balanced translocation between chromosomes 2 and 20, and they concluded that the Alagille gene may be a single dominant gene at 20p12.2. Our patient had a small deletion but the morbidity was very serious. In comparison with the others, we found that the severity of the morbidity does not reflect the extent of the deletion involved. Additionally, the frequency of cytogenetically visible deletions in Alagille syndrome is lower [Zhang et al., 1990; Desmaze et al., 1992] than that in the other contiguous gene syndromes [Nicholls et al., 1989; Driscoll et al., 1993]. Unfortunately, we have no suitable FISH probes to decide the accurate breakpoints in our patient. If the breakpoint is interpreted to be at 20p12.2 and p13, the breakpoint in three cases described by Spinner et al. [1994] and our patient would be consistent with the shortest region of overlap, and the Alagille gene would be narrowed down further probably to 20p12.2.

There have been two alternative hypotheses for the cause of Alagille syndrome: contiguous gene syndrome vs. single gene defect [Spinner et al., 1994]. Familial occurrence of the 20 bp deletion is known in two families [Anad et al., 1990; Spinner et al., 1994], and the present family is the third one of such a familial transmission. The mother of our patient was a phenotypically normal carrier with an insertion of a 20p11.23-p12.2 (or p12.2-p13) segment into 7q11.23. The transmission of the deleted chromosome 20 from the mother caused Alagille syndrome in the patient, and the same may be true





c.

Fig. 3. Cytogenetic abnormalities in the case: 46,XY,der(20)dir ins(7;20)(q11.23;p11.23p12.2 or p12.2p13)mat. **a** and **b:** der(20) of the patient from two cells showing the deleted fragment indicated by arrows. **c:** Idiogram of the der(20).

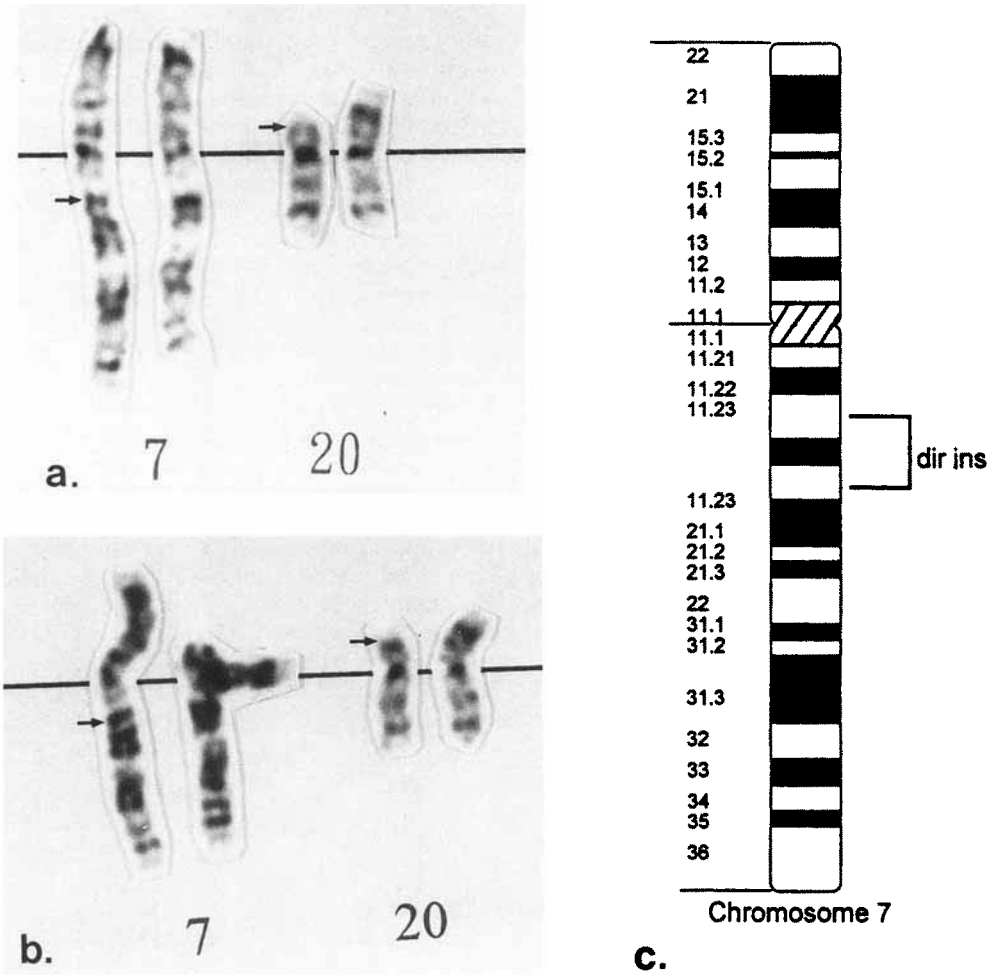


Fig. 4. Cytogenetic abnormalities showing a balanced translocation present in mother: 46,XX,dir ins(7;20)(q11.23;p11.23p12.2 or p12.2p13). **a** and **b:** Chromosome 7 and 20 of the mother from two cells showing the translocated fragment indicated by arrows. **c:** Idiogram of the maternal chromosome 7.

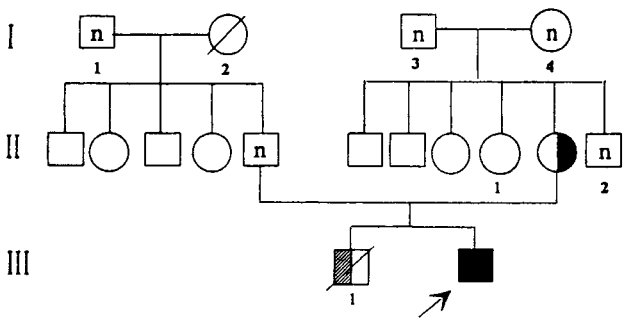


Fig. 5. Pedigree. The propositus had clinically demonstrated Alagille syndrome. His elder brother (III-1) probably had Alagille syndrome and died of hepatic failure at age 3 years. Individuals with normal chromosomes (n) are indicated. I-2 died at age 50 years of rectal carcinoma. I-3 had history of coronary artery disease. I-4 had diabetes mellitus. II-1 had cleft of lip and palate. ◑, chromosome aberration; ■, Alagille syndrome; ◧, possible Alagille syndrome.

in his elder brother. Therefore, if the syndrome is a single gene defect, the putative gene responsible for Alagille syndrome would not be located at the insertion breakpoints but located within the deletion extent. Further molecular study and linkage analysis may elucidate the underlying defect.

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